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(54) **NOVEL METHYLENEBISPHOSPHONIC ACID DERIVATIVES**

NEUE METHYLENBISPHOSPHONSÄUREDERIVATE

NOUVEAUX DERIVES D'ACIDE METHYLENEBIPHOSPHONIQUE

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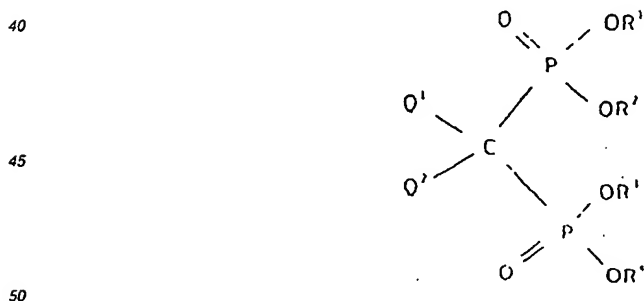
(56) References cited:
EP-A- 0 098 567 **EP-A- 0 252 504**
DE-C- 1 617 118 **US-A- 3 303 139**
US-A- 3 683 080 **US-A- 3 957 858**
US-A- 4 634 691

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Description

- [0001] The invention concerns novel methylenebisphosphonic acid derivatives, in particular novel alkyl or aminoalkyl substituted methylenebisphosphonic ester acids and ester salts, processes for the preparation of these novel compounds, as well as pharmaceutical compositions comprising these novel compounds.
- [0002] Several publications disclose methylenebisphosphonic acids, their salts and some tetraesters, but there are only a few disclosures of corresponding partial esters, tri-, di- and monoesters.
- [0003] The preparation of tetraesters of methylenebisphosphonic acids has been described in the publications: EP 0221 611; J. Am. Chem. Soc. 78, (1956) 4450; J. Chem. Soc. (1959) 2266 and 2272; J. Am. Chem. Soc. 84 (1962) 1876; J. Org. Chem. 35, (1970) 3149; J. Org. Chem. 36, (1971) 3843 and Phosphorus, Sulfur and Silicon 42, (1989) 73.
- [0004] The publications EP-A-0098567, EP-A-0252504, US 3,683,080 and US 4,634,691 describe diphosphonic acid derivatives for the treatment of disorders relating to calcium metabolism, e.g. diseases of the skeletal system. The said EP-applications refer in a general manner to the formation of diesters from corresponding tetraesters, but provide no specific example, nor any information to the activity of such esters. The US patents describe the use of diphosphonic tetraacids, or tetraesters or salts thereof. In the US-patents 3,957,858 and 3,303,139 as well as the DE-patent 1617118 the use of diphosphonic acids, as well as some partial esters thereof, are described as metal complexation agents, for example as complex forming agents in the treatment of water or as fire retardants.
- [0005] According to the invention it has been discovered that the novel partial esters of substituted methylenebisphosphonic acids and their salts in many cases exhibit more favourable properties than the corresponding bis-phosphonic acids and salts due to their better kinetics and availability; their ability to participate as complex formers in the regulation of the metabolism of the organism being maintained.
- [0006] They are well suited for the treatment of disorders relating to the metabolism of calcium and of other, especially bivalent metals. They may be used both for the treatment of diseases in the skeletal system, especially of bone formation and resorption disorders, such as of osteoporosis and Paget's disease, as well as for the treatment of diseases in the soft tissues, such as of deposition and mineralisation conditions and bone formation disorders.
- [0007] On the other hand, being pyrophosphate analogs, the new substituted methylenebisphosphonic acid derivatives are also suitable for the treatment of disorders in the (pyro)phosphate functions of the organism, including the functions, wherein an active, but disturbance-prone or wrongly active organic part is attached to (pyro)phosphate or acts as a metal complex or a combination of the last mentioned.
- [0008] The novel bisphosphonates regulate either directly or over an indirect mechanism the quality and level of cations and/or pyrophosphate compounds freely present in the body fluids as well as of that binding to, active in and liberated from the tissues. Thus they are able to regulate the cellular metabolism, growth and destruction. Consequently they are useful for the treatment of e.g. cancer of the bone and metastases thereof, ectopic calcifications, urolithiasis, rheumatoid arthritis, bone infections and bone degradation.
- [0009] Typical for the novel substituted methylenebisphosphonates is a selective desired and controlled action, providing for a better therapeutic index.
- [0010] The invention concerns novel methylenebisphosphonic acid derivatives of the general formula I



in which formula one or two of the groups R^1 , R^2 , R^3 and R^4 are independently straight or branched C_1 - C_{10} -alkyl, and the remaining groups R^1 , R^2 , R^3 and R^4 are hydrogen,

R^1 is hydroxyl,

R^2 is straight or branched C_1 - C_{10} -alkyl, cyclohexyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-aminoethyl, 3-aminopropyl, (3-dimethylamino)propyl, or 5-aminopentyl,

including the stereoisomers, such as the geometrical isomers and the optically active isomers, of the compounds, as well as the pharmacologically acceptable salts of the compounds.

[0011] The groups R^1 , R^2 , R^3 and R^4 are independently a straight or branched alkyl group and they contain 1 to 10, preferably 1 to 7, and advantageously 1 to 4, carbon atoms.

[0012] The group Q^2 contains as the alkyl group, 1 to 10, preferably, however, 1 to 4, carbon atoms.

[0013] Salts of the compounds of the formula I are especially their salts with pharmaceutically acceptable bases, such as metal salts, for example alkalimetal salts, especially lithium, sodium and potassium salts, alkaline earth metal salts, such as calcium or magnesium salts, copper, aluminium or zinc salts, as well as ammonium salts with ammonia or with primary, secondary and tertiary, both aliphatic and alicyclic as well as aromatic amines, and quaternary ammonium salts, such as halides, sulphates and hydroxides, salts with aminoalcohols, such as ethanol-, diethanol- and triethanolamines, tris(hydroxymethyl)-aminomethane, 1- and 2-methyl- and 1,1-, 1,2- and 2,2-dimethylaminoethanols, N-mono- and N,N-dialkylaminoethanols, N-(hydroxymethyl- and ethyl)-N,N-ethanediamines, as well as amino crown ethers and cryptates, and heterocyclic ammonium salts, such as azetidinium, pyrrolidinium, piperidinium, piperazinium, morpholinium, pyrrolium, imidazolium, pyridinium, pyrimidinium, quinolinium, etc., salts.

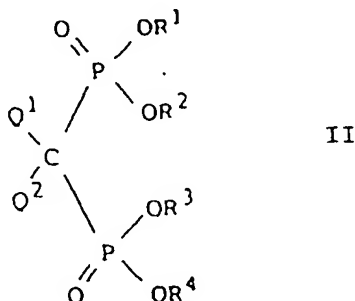
[0014] Especially good results have been obtained with the mono- or dimethyl-, mono- or diethyl-, mono- or diisopropyl esters, or corresponding mixed diesters, wherein Q^2 is for example methyl, ethyl, propyl, isopropyl, 2,2-dimethylpropyl or butyl, or [3-methyl(pentyl)amino]propyl.

[0015] Examples of such compounds are:

(1-Hydroxyethylidene)bisphosphonic acid monomethyl and monoethyl ester
 (1-hydroxypentylidene)bisphosphonic acid monomethyl ester,
 (1-hydroxyethylidene)bisphosphonic acid dimethyl and diethyl ester,
 (2,2-dimethyl-1-hydroxypropylidene)bisphosphonic acid monomethyl ester
 [hydroxy(cyclohexyl)methylidene]bisphosphonic acid monomethyl ester,
 (1,3-dihydroxypropylidene)bisphosphonic acid monoethyl ester,
 (3-amino-1-hydroxypropylidene)bisphosphonic acid monomethyl and monoethyl ester,
 (4-amino-1-hydroxybutylidene)bisphosphonic acid monomethyl and monoethyl ester,
 (6-amino-1-hydroxyhexylidene)bisphosphonic acid monomethyl- and monoisopropyl ester,
 (3-amino-1-hydroxypropylidene)bisphosphonic acid P,P'-dimethyl and P,P'-diethyl ester,
 (4-amino-1-hydroxybutylidene)bisphosphonic acid P,P'-dimethyl- and P,P'-diethyl ester,
 [(4-dimethylamino)-1-hydroxybutylidene]bisphosphonic acid monoethyl ester, and
 [(3-methyl(pentyl)amino)-1-hydroxypropylidene]bisphosphonic acid monomethyl ester.

[0016] The invention concerns also processes for the preparation of the compounds of the formula I, which is characterized in that

a) a methylenebisphosphonic acid tetraester of the formula II



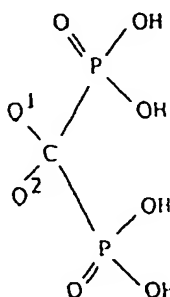
in which formula Q^1 and Q^2 have the same meaning as above, and R^1 , R^2 , R^3 and R^4 have the same meaning as above, or triloer alkyl silyl, except hydrogen, is selectively hydrolysed

- to a diester corresponding to the formula I, wherein two of the groups R^1 , R^2 , R^3 and R^4 have the meaning of hydrogen, or a salt thereof, or
- to a monoester corresponding to the formula I, wherein three of the groups R^1 , R^2 , R^3 and R^4 have the meaning of hydrogen, or a salt thereof, or

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b) a bisphosphonic acid of the formula

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VI I

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or a metal or ammonium salt thereof, or the corresponding acid tetrachloride, wherein Q^1 and Q^2 have the same meaning as above, is esterified selectively by reacting the same with an esterification reagent corresponding to the desired groups R^1 , R^2 , R^3 and R^4 ,

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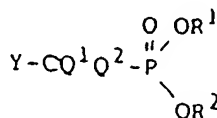
- to a monoester corresponding to the formula I, wherein three of the groups R^1 , R^2 , R^3 and R^4 have the meaning of hydrogen, or
- to a diester corresponding to the formula I, wherein two of the groups R^1 , R^2 , R^3 and R^4 have the meaning of hydrogen,

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or to the corresponding ester salts of the said partial esters, or

c) a phosphonate having the formula

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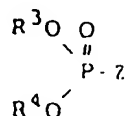


I X

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is reacted with an activated phosphate or a hydrogen phosphonate corresponding to the formula X

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X

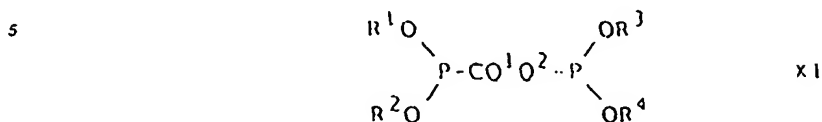
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wherein in the formulas Y is hydrogen, hydroxy or halogen or other leaving group, Z is hydrogen, halogen, acyloxy, sulphonyloxy, alkoxy or aryloxy, and R^1 to R^4 and Q^1 and Q^2 have the same meaning as before, or Q^1 and Q^2 form a double-bonded oxygen, or is reacted with a phosphite corresponding to the formula X, or

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d) a bisphosphonate corresponding to the formula I, which instead of Q^2 has a carbanion site, is reacted with ω -leaving group substituted Q^2 , or a bisphosphonate corresponding to the formula I, which instead of Q^2 contains a leaving group, is reacted with a ω -carbanion corresponding to Q^2 , or a (Q^2-C_1) - ω -carbanion is added by Michael addition in alkylidenebisphosphonates, or

e) a bisphosphonite compound having the formula



wherein R^1 , R^2 , R^3 and R^4 and Q^1 and Q^2 have the same meaning as in the formula I, or the corresponding hydrogen phosphonate compound, is oxidized to a compound of the formula I, and if desired, the partial ester acids obtained according to a) to e) are converted to partial ester salts, or the partial ester salts obtained are converted to the partial ester acids, and/or, if desired, a compound according to the formula I obtained is converted into some other compound according to the formula I by hydrolyzing, esterification or transesterification.

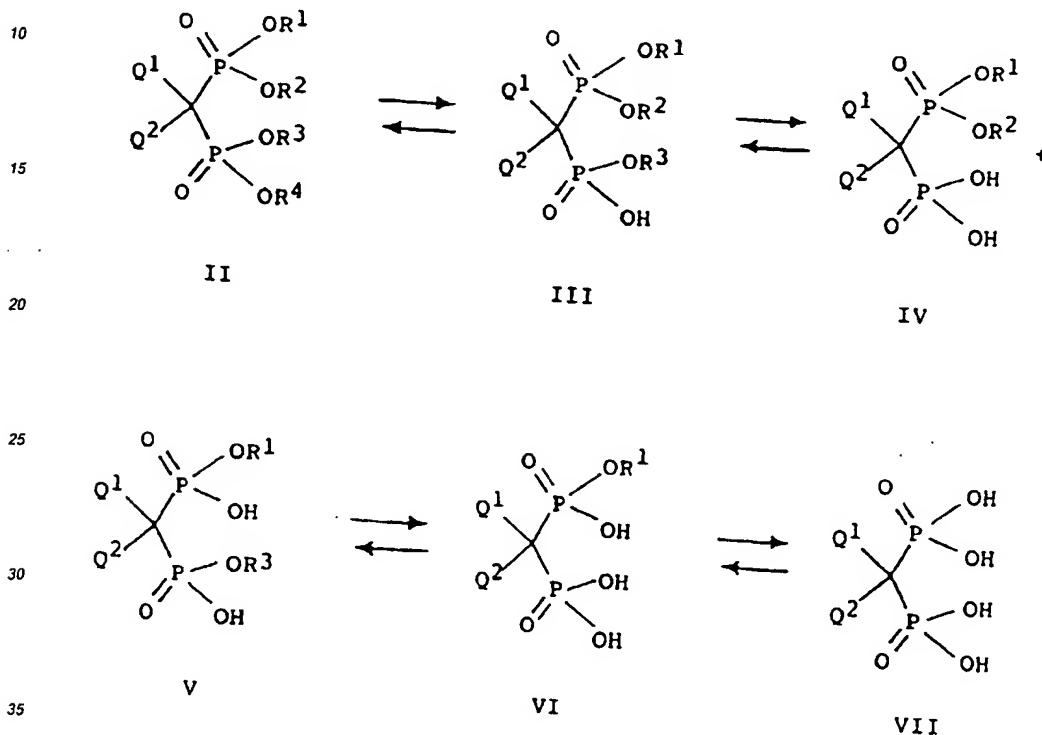
[0017] In a trilower alkyl silyl group lower alkyl contains 1 to 4 carbon atoms, and is especially methyl, ethyl, isopropyl, butyl or tert-butyl, whereby also different combinations of lower alkyls come into question, such as dimethyl tert-butyl, methyl diisopropyl.

[0018] According to one process the compounds are thus prepared by selective hydrolysis of the tetraesters corresponding to the formula I. Thus a tetraester is used as the starting material, wherein the groups R^1 to R^4 and Q^1 and Q^2 have the same meaning as above and this tetraester is hydrolyzed stepwise to the triester III, diester IV and V and the monoester VI. If necessary, the partial ester or its salt may be isolated and purified by extraction, fractional crystallization or chromatographically, and if desired, a free acid may be converted into a salt or a salt into the free acid.

[0019] This reaction is shown in the appended scheme 1 (the reaction takes place in the direction of the upper arrow).

Scheme 1

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40 [0020] The hydrolysis of the tetraesters II may be carried out by treating both with an acid and a base, using thermal cleaving, and in certain cases also using water, alcohols, or other neutral or non-neutral transalkylation, -silylation or -arylation reagents. The hydrolysis takes place advantageously at a temperature range of 10 to 150°C. The acids are advantageously conventional inorganic acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, and Lewis acids, such as boron trifluoride etherate, titanium tetrachloride, etc., as well as a number of organic acids, such as oxalic acid, formic acid, acetic acid and other carboxylic acids, methanesulphonic acid and other sulphonic acids, such as tosyl acid, further chlorine and fluorine substituted carboxylic and sulphonic acids, such as trichloroacetic acid and trifluoromethane sulphonic acid, and their aqueous solutions.

45 [0021] The bases are advantageously alkali and ammonium hydroxides and ammonia and the aqueous solutions thereof, as well as a number of amines, such as primary, secondary and tertiary amines, such as e.g. diethyl-, triethyl-, diisopropyl- and tributylamine, aniline, N- and N,N-alkyl substituted anilines and heterocyclic amines, such as pyridine, morpholine, piperidine, piperazine etc., and hydrazines, such as N,N-dimethyl hydrazine.

50 [0022] In addition, acids and bases bound to a solid substrate may be used, such as Amberlites, either in the presence of an organic solvent or water or various solvent mixtures, or in the absence thereof.

55 [0023] Further by treating with certain alkali metals, such as sodium and lithium, or with suitable inorganic salts, such as with sodium iodide, lithium bromide, ammonium chloride and NaBr/PTC, the ester group may be converted to its corresponding salt, such as to the sodium, ammonium and lithium salt.

[0024] Thermal cleaving usually takes place at a temperature of about 100 to 400°C, usually, however, at a temperature of not more than 250°C. The presence of a suitable catalyst, such as an acid or an acid solution, or a quaternary

ammonium salt, makes it possible for a reaction to take place faster and at a lower temperature. Certain active substituents, such as benzyl and allyl, may be removed by catalytic reduction or electrolytically.

[0025] To improve solubility and to control the reaction temperature during the reactions, organic, inert solvents, such as hydrocarbons, lower alcohols and stable ketones and esters, alkyl halides, such as chloroform, dichloromethane and -ethane, ethers, such as dioxan, dimethoxyethane, diglyme, acetonitrile, etc., may be used as co-solvents.

[0026] When the groups R^1 to R^4 in the tetraester according to the formula II are the same, the hydrolysis takes place stepwise, and it is interrupted when the concentration of the desired partial ester is at its greatest.

[0027] In order to prepare a specific partial ester structure, it is advantageous to use a tetraester of the formula II wherein the ester groups are not the same, but groups which are different with respect to the hydrolysis rate. It has, for example, been discovered that the hydrolysis rate of alkyl and silyl esters is dependant on the structure as follows:

silyl > tert > sec > prim

[0028] It is possible to affect the hydrolysis rate by changing also the size and shape of the alkyl and silyl substituent as well as by electronical factors. It is often possible to perform a transesterification in order to change the stepwise hydrolysis of the different ester sites. Especially the methyl ester may be advantageously converted to the corresponding acid over a silyl ester.

[0029] Pure partial esters may thus be prepared in an advantageous manner by performing a selective hydrolysis of mixed esters of the formula I, which have been prepared using ester groups which are advantageous from the point of view of hydrolysis.

[0030] Also other selective hydrolysis reactions known especially from phosphate and monophosphonate chemistry may be used.

[0031] The progress of the hydrolysis may be followed for example chromatographically or by means of ^{31}P -NMR spectroscopy. The reaction may be interrupted when the level of the desired partial ester is at its greatest and the product may be isolated from the reaction mixture either as the free acid or as a salt by precipitation, extraction or chromatographically, and the salt form may be converted to the free acid or the free acid to its salt.

[0032] The compounds according to this invention may be prepared also by selective esterification of bisphosphonic acids in accordance with the above mentioned reaction Scheme 1 (the reaction takes place in the direction of the lower arrow).

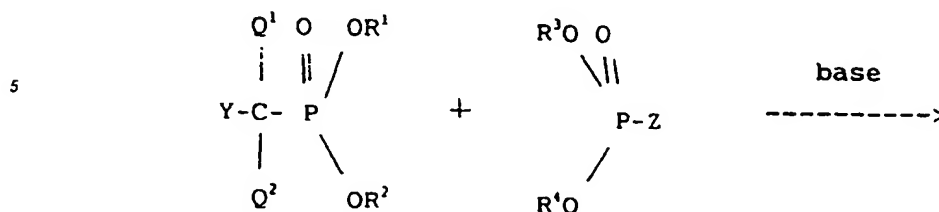
[0033] A tetraacid according to the formula VII (R^1 to $R^4 = \text{H}$) may thus be as a starting material used, which can be as the free acid or is in the form of a salt, such as a metal or ammonium salt, or the corresponding phosphonic acid tetrachloride may be used, and depending on the desired end result, 1 to 4 equivalents of the desired aliphatic or aromatic alcohol, or the corresponding activated alkylation, silylation and arylation reagents, such as ortoesters, ketene acetals and other suitable transfer reagents for alkyl-, silyl- and aryl groups, such as diazo compounds, active carboxylic acid esters, sulphates, etc. The reaction is usually performed under anhydrous conditions, preferably in the temperature range of 0. to 150°C , or when using an inert co-solvent, at the boiling point thereof.

[0034] The esters II to IV may also be prepared in a nucleophilic substitution reaction between the bisphosphonate anion, often the ammonium salt, and an organic halide or sulphonate, or in a condensation reaction between a phosphonic acid group and a suitable alcohol or a phenol using a reagent for cleaving off water, such as carbodiimides.

[0035] Pure partial esters, also mixed esters, may thus be prepared by selective esterification, if necessary stepwise, of tetraacids of the formula VII. Also other selective esterification reactions may be used known primarily from phosphate and monophosphonate chemistry.

[0036] The progress of the esterification reactions may be followed, for example, chromatographically or using ^{31}P -NMR and the reaction is interrupted when the content of the desired partial ester is at its greatest and this is isolated from the reaction mixture by precipitation, extraction or chromatographically and, if desired, a salt form obtained is converted to the free acid or the free acid is converted to its salt.

[0037] Partial esters according to the invention may also be prepared by constructing the P-C-P frame from its parts



wherein in the formula Y is hydrogen, hydroxy or halogen or or other leaving group, Z is halogen, acyloxy, sulphonyloxy, alkoxy, or aryloxy, and R¹ to R⁴ and Q¹ and Q² have the meaning given above, or Q¹ and Q² are double-bonded oxygen. As the base, for example, sodium hydride, butyl lithium or lithium diisopropylamide may be used. In the starting material optionally present free acid sites (one of the groups R¹ to R⁴ = H) have to be neutralized, by using a sufficient amount of base, prior to the coupling reaction. Also active sites in the groups Q¹ and Q² have to be neutralized or the said active site has to be protected with a protecting group.

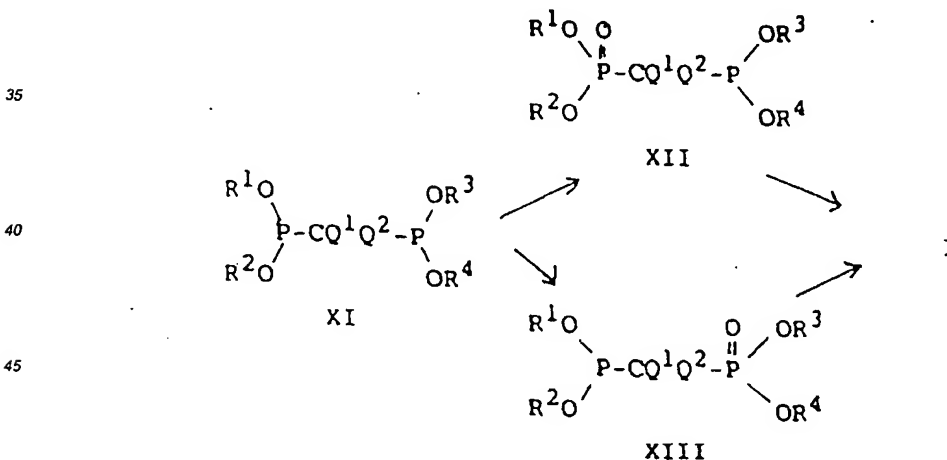
[0038] Also the Michaelis-Arbuzov reaction may be used, whereby the second reacting compound is a phosphite, or the Michaelis-Becker reaction, whereby Z is hydrogen.

[0039] In certain instances the group Q¹ may be introduced by an exchange reaction, or an oxidation or reduction reaction, whereby hydroxyl may be obtained from hydrogen, halogen or amino.

[0040] Q² may also be brought into the molecule either by a reaction of a bisphosphonate carbanion or corresponding reaction involving C-halogen or other leaving group, whereby the Q²-reagent is ω-substituted with a leaving group, or correspondingly is a ω-carbanion.

[0041] The compounds according to the invention may also be prepared by applying the Michael addition to alkylidene phosphonates described in the EP patent application 0 221 611.

[0042] The esters according to the invention may also be prepared from P-C-P-structures at a lower oxidation level by oxidation



whereby in the formulas R¹ to R⁴ and Q¹ and Q² have the same meaning given above, and whereby the phosphonite structure may exist in an equilibrium with the hydrogenphosphonate structure. All conventional oxidation agents, or their solutions, such as hydrogen peroxide, perhalogen compounds, peracids, permanganate etc., come into question.

[0043] The partial esters of bisphosphonic acid according to the invention may also be prepared from other partial esters by performing an intra- or intermolecular exchange reaction.

[0044] The tetraesters II and corresponding tetraacids IV used as starting materials in the above reactions may be prepared by processes known as such from literature by constructing the P-C-P frame from its parts, for example using the above mentioned Michaelis-Becker-, Michaelis-Arbuzov- or carbanion reaction, also stepwise, whereby the groups

R¹ to R⁴ may be chosen and advantageously introduced as parts of the bisphosphonate taking into account the structure of the desired partial ester, and by suitably substituting this frame or an anion obtained therefrom, for example by an alkylation or an addition reaction.

[0045] Taking into account the preparation of a desired partial ester, the prepared tetraesters may, if necessary, be converted to other suitable tetraesters using exchange reactions. Thereby the groups OR¹ to OR⁴ may be exchanged directly or over the corresponding phosphono-chloride or by applying other known processes.

[0046] Optically active partial esters may be best prepared by using known optically active compounds, such as optically active alcohols, in the preparation of the above mentioned starting materials, intermediates and end products, or in the exchange reactions.

[0047] The properties of the compounds according to the invention have been tested in the following test systems.

[0048] Firstly the physico-chemical effects of the compounds according to the invention were determined as regards their calcium phosphate crystal formation and precipitation inhibiting activity [Shinoda et al (Calc Tiss Int 1983; 35:87) and Jung et al. (Calc Tiss Res 1973; 11:269) (Table 1).

[0049] In addition, the parathyroid hormone stimulated bone resorption inhibition activity in vitro in mouse calvaria, as well as inhibition of retinoid induced bone resorption in thyroparathyroidectomised rats in vivo were determined (Reynolds & Dingle (Calc Tiss Res 1970; 4:339, and Trechsel et al. (J Clin Invest 1987; 80:1679)) (Table 2).

Table 1

Effect of bisphosphonates and their derivatives on hydroxyapatite		
Compound	Binding, Ki μ M	Inhibition of growth
Clodronate	1.3	+++
Etidronate	0.9	+++
(1-Hydroxypentylidene)bisphosphonate	2.5	+++
Monoisopropyl-(1-hydroxyethylidene)bisphosphonate	7.3	+++
Monoisopropyl-(1-hydroxypentylidene)bisphosphonate	15.4	++
Monomethyl-(1-hydroxypentylidene)bisphosphonate	11.8	+++

+++ = complete inhibition at 100 μ M

++ = almost complete inhibition at 100 μ M

+ = slight inhibition at 100 μ M.

Table 2

Antiresorptive activity Inhibition of resorption (%)			
	100 μ M	1000 μ M	150 μ mole/kg
	in vitro		in vivo
Clodronate	43	ND	64
(1-Hydroxypentylidene)bisphosphonate	56	ND	ND
Monomethyl-(1-hydroxypentylidene)bisphosphonate	7	47	52

ND = Not determined.

[0051] From the tables the superiority of the compounds of the invention, especially their better relative in vivo-antiresorptive activity is apparent.

[0052] The partial esters of substituted bisphosphonic acids of the formula I may be used as pharmaceuticals as such, or as their pharmacologically suitable salts, such as the alkali or ammonium salts. Such salts may be prepared by reacting the ester acids with the corresponding inorganic or organic bases. Depending on the reaction conditions, the ester salts may be formed also directly in the above mentioned reactions.

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[0053] The new compounds I according to this invention may be administered enterally or parenterally. All conventional administration forms, such as tablets, capsules, granules, syrups, solutions, implants and suspensions come into question. Also all adjuvants for manufacture, dissolution and administration of the preparation, as well as stabilizers, viscosity regulating and dispersion agents and buffers, may be used.

5 [0054] Such adjuvants include i.a. tartrate and citrate buffers, alcohols, EDTA and other nontoxic complexing agents, solid and liquid polymers and other sterile substrates, starch, lactose, mannite, methylcellulose, talc, silicic acids, fatty acids, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and, if desired, flavouring and sweetening agents.

10 [0055] The dosage depends on several factors, for example on the manner of administration, species, age and individual condition. The daily doses are about 0.1 to 1000 mg, usually 1 to 100 mg per person, and they may be administered as a single dose or may be divided into several doses.

[0056] In the following, examples of a typical capsule and a tablet are given:

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Capsule	mg/caps.
Active ingredient	10.0 mg
Starch	20.0 mg
Magnesium stearate	1.0 mg
Tablet	
Active ingredient	40.0 mg
Microcrystalline cellulose	20.0 mg
Lactose	67.0 mg
Starch	10.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

[0057] For medicinal use, also an intramuscularly or parenterally administered preparation may be made, for example an infusion concentrate, wherein as adjuvants eg. sterile water, phosphate buffer, NaCl, NaOH or HCl or other known pharmaceutical adjuvants suitable for the purpose may be used.

[0058] The compounds in ester-acid form according to the invention are liquids or waxy substances, usually soluble in organic solvents and in some instances in water. The ester salts are solid, crystalline or typically powdery substances which usually dissolve well in water, in some instances in organic solvents, but only some structure types being poorly soluble in all solvents. The compounds are very stable, also in their neutral solutions at room temperature.

40 [0059] The structure of the compounds may easily be verified with ^1H -, ^{13}C - and ^{31}P -NMR-spectroscopy and FAB-massspectrometry, or when silylated, with EI-massspectrometry. For concentration and impurity determinations ^{31}P -NMR-spectroscopy is very suitable (85 % H_3PO_4 $\delta = 0$). Also for polar compounds as such ion exchange and exclusion-HPLC may be used and for tetraesters and silylated ester acid derivatives GLC or GC/MS may be used. From the compounds sodium and other metals were determined separately as well as the possible crystal water content. From the

45 the amine salts, nitrogen was determined.

[0060] The following examples illustrate the invention without limiting the same in any way.

Preparation of starting materials

50 Example A

Preparation of (1-hydroxyethylidene)bisphosphonic acid tetramethyl ester

55 [0061] Dimethylphosphite (0.047 moles) and dibutylamine (0.0026 moles) were dissolved in diisopropylether and to the solution dimethyl acetylphosphonate (0.047 moles) was added at 0 °C. The solution was stirred at 0 °C for 4 hours and at room temperature for a day. The product was filtered, washed with diisopropylether and dried. Yield was 8.3 g (67 %; ^{31}P -NMR 22.95 ppm; CDCl_3).

[0062] Dimethyl acetylphosphonate used as the starting material may prepared in the following manner:

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[0063] To acetyl chloride (0.31 moles) was added at 0 °C slowly trimethylphosphite (0.3 moles). The mixture was stirred for 5 hours at 0 °C and left standing over night at room temperature. The product was distilled at reduced pressure, b.p. 96-100 °C/9 mm Hg. Yield 39 g (86 %).

[0064] In the corresponding manner may be prepared:

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(1-Hydroxyethylidene)bisphosphonic acid P,P-dimethyl P',P'-diethyl ester from dimethyl acetylphosphonate and diethylphosphite (31-P NMR 20.54/23.32 ppm, J=39.4 Hz; CDCl₃).

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(1-Hydroxyethylidene)bisphosphonic acid P,P-dimethyl P',P'-bis(trimethylsilyl) ester from dimethyl acetylphosphonate and bis(trimethylsilyl)phosphite (31-P NMR 2.89/12.93 ppm, J=44.1 Hz; CDCl₃).

(1-Hydroxyethylidene)bisphosphonic acid P,P'-dimethyl P,P'-bis(trimethylsilyl) ester from methyl(trimethylsilyl) acetylphosphonate and methyl(trimethylsilyl)phosphite (31-P NMR -0.50 ppm; CDCl₃).

15

(1-Hydroxypentylidene)bisphosphonic acid P,P-dimethyl P',P'-diethyl ester from dimethyl pentanoylphosphonate and diethylphosphite (31-P NMR 20.9/23.39 ppm, J=37.0 Hz; CDCl₃).

(1-Hydroxypentylidene)bisphosphonic acid P,P-dimethyl P',P'-diisopropyl ester from dimethyl pentanoylphosphonate and diisopropylphosphite (31-P NMR 16.63/21.56 ppm, J=41.0 Hz; CDCl₃).

20

(1-Hydroxypentylidene)bisphosphonic acid tetramethyl ester from dimethyl pentanoylphosphonate and dimethylphosphite (31-P NMR 20.62 ppm; CDCl₃).

25

(1-Hydroxy-2,2-dimethylpropylidene)bisphosphonic acid tetramethyl ester from dimethyl pivaloylphosphonate and dimethylphosphite (31-P NMR 23.80 ppm; CDCl₃).

(1-Hydroxy-2,2-dimethylpropylidene)bisphosphonic acid P,P-dimethyl P',P'-diethyl ester from dimethyl pivaloylphosphonate and diethylphosphite (31-P NMR 20.57/23.46 ppm, J=31.3 Hz; CDCl₃).

30

(Hydroxy(cyclohexyl)methylidene)bisphosphonic acid tetramethyl ester from dimethyl cyclohexanoylphosphonate and dimethylphosphite (31-P NMR 23.13 ppm; CDCl₃).

[0065] In addition may be prepared:

35

(1-Hydroxyethylidene)bisphosphonic acid P,P-dimethyl P',P'-diisopropyl ester from diisopropyl acetylphosphonate and dimethylphosphite (31-P NMR 18.69/23.73 ppm, J=40.4 Hz; CDCl₃).

(1-Hydroxyethylidene)bisphosphonic acid P,P-diethyl P',P'-diisopropyl ester from diisopropyl acetylphosphonate and diethylphosphite (31-P NMR 16.55/18.95 ppm, J=41.7 Hz; CDCl₃).

40

(1-Hydroxypentylidene)bisphosphonic acid P,P-dimethyl P',P'-diisopropyl ester from diisopropyl pentanoylphosphonate and dimethylphosphite (31-P NMR 16.63/21.56 ppm, J=41.0 Hz; CDCl₃).

45

(1-Hydroxyethylidene)bisphosphonic acid P,P-dimethyl P',P'-dibutyl ester from dibutyl acetylphosphonate and dimethylphosphite (31-P NMR 20.40/23.33 ppm, J=40.1 Hz; CDCl₃).

(1-Hydroxypentylidene)bisphosphonic acid P,P-diethyl P',P'-diisopropyl ester from diisopropyl pentanoylphosphonate and diethylphosphite.

50

[(4-Dimethylamino)-1-hydroxybutylidene]bisphosphonic acid P-ethyl [P,P',P'-tris(trimethylsilyl)] ester from bis(trimethylsilyl) (4-dimethylamino)butanoylphosphonate and ethyl(trimethylsilyl)phosphite.

[(3-methyl(pentyl)amino)-1-hydroxypropylidene]bisphosphonic acid P-methyl [P,P',P'-tris(trimethylsilyl)] ester from methyl(trimethylsilyl) [3-methyl(pentyl)amino] propanoylphosphonate and bis(trimethylsilyl)phosphite.

55

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Example B

Preparation of (1-hydroxypentylidene)bisphosphonic acid tetramethyl ester

- 5 [0066] A mixture of (1-hydroxypentylidene)bisphosphonic acid (0.1 moles) and trimethyl orthoformate (0.5 moles) was heated for 6 hours at 100 °C. Thereafter the methanol formed in the reaction and unreacted orthoformate was distilled off. The residue was the tetramethyl ester, yield 25 g (82 %, ³¹P NMR 20.62 ppm; CDCl₃).

[0067] In the same manner may be prepared:

- 10 (1-Hydroxyethylidene)bisphosphonic acid tetramethyl ester (³¹P NMR 22.95 ppm; CDCl₃).
(1-Hydroxy-2,2-dimethylpropylidene)bisphosphonic acid tetramethyl ester (³¹P NMR 23.80 ppm; CDCl₃).
(4-Amino-1-hydroxybutylidene)bisphosphonic acid tetramethyl ester.
15 (3-Amino-1-hydroxypropylidene)bisphosphonic acid tetramethyl ester.
(3-Amino-1-hydroxypropylidene)bisphosphonic acid tetraethyl ester.
20 [3-(Dimethylamino)-1-hydroxypropylidene]bisphosphonic acid tetramethyl ester.
(6-Amino-1-hydroxyhexylidene)bisphosphonic acid tetraethyl ester (³¹P NMR 23.1 ppm; CDCl₃).
(6-Amino-1-hydroxyhexylidene)bisphosphonic acid tetramethyl ester.
25 [3-(Dimethylamino)-1-hydroxypropylidene]bisphosphonic acid tetraethyl ester.
[(3-Benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid tetramethyl ester.
30 [(4-Benzyloxycarbonylamino)-1-hydroxybutylidene]bisphosphonic acid tetraethyl ester.

Example C

Preparation of (1-hydroxy-2,2-dimethylpropylidene)bisphosphonic acid tetramethyl ester

- 35 [0068] Into a chloroform solution of trimethyl phosphite (0.1 moles) and dimethyl phosphite (0.1 moles) pivaloyl chloride (0.1 moles) dissolved in chloroform was added slowly at 0 °C. The mixture was heated at 80 °C for 10 hours. The solvent was evaporated at reduced pressure, and the product precipitated by adding diisopropylether. Yield 24 g (80 %, ³¹P NMR 23.80 ppm; CDCl₃).

40 [0069] In the same manner may be prepared

- (4-(N-phtalimidyl)-1-hydroxybutylidene)bisphosphonic acid tetramethyl ester (³¹P NMR 19.90 ppm; CDCl₃).
(3-(N-phtalimidyl)-1-hydroxypropylidene)bisphosphonic acid tetraethyl ester.
45 [3-(Benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid tetramethyl ester.

Example 1

50 Preparation of (1-hydroxyethylidene)bisphosphonic acid P',P'-diisopropyl ester and its disodium salt

- [0070] Into a acetonitrile solution of (1-hydroxyethylidene)bisphosphonic acid P,P-dimethyl P',P'-diisopropyl ester (0.02 moles) and sodium iodide (0.04 moles) chlorotrimethylsilane (0.042 moles) was added slowly at room temperature. The solution was stirred for 2 hours, whereafter the solvent was evaporated at reduced pressure. The evaporation
55 residue was dissolved in a small amount of warm water, and the solution was made alkaline with a dilute sodium hydroxide solution. The product was precipitated by adding ethanol (³¹P NMR 16.80/23.24 ppm, J=37.6 Hz; D₂O).

[0071] In a corresponding manner the following esters and their sodium salts may be prepared:

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- (1-Hydroxyethylidene)bisphosphonic acid P,P-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 13.25-32.20 ppm, J=29.0 Hz; D₂O).
- 5 (1-Hydroxyethylidene)bisphosphonic acid P',P'-dibutyl ester from the corresponding P,P-dimethyl P',P'-dibutyl ester (31-P NMR 27.95/28.97 ppm, J=31,2 Hz; D₂O).
- (1-Hydroxysthylidene)bisphosphonic acid P',P'-diethyl ester from the corresponding P,P-dimethyl P',P'-diethyl ester (31-P NMR 13.41/29.68 ppm, J=29.9 Hz; D₂O).
- 10 (4-Amino-1-hydroxybutylidene)bisphosphonic P,P-dimethyl ester from the corresponding tetramethylester.
- (6-Amino-1-hydroxyhexylidene)bisphosphonic acid P,P-dimethyl ester from the corresponding tetramethyl ester.
- 15 [4-(N-Phtalimidyl)-1-hydroxybutylidene]-bisphosphonic acid P,P-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 15.76/23.8 ppm, J=23.7 Hz; D₂O).
- (3-Amino-1-hydroxypropylidene)bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester.
- 20 (3-Amino-1-hydroxypropylidene)bisphosphonic acid P,P-dimethyl ester from the corresponding tetramethyl ester.
- (1-Hydroxypentylidene)bisphosphonic acid P',P'-diisopropyl ester from the corresponding P,P-dimethyl P',P'-diisopropyl ester (31-P NMR 14.60/26.80 ppm, J=31.7 Hz; D₂O).
- 25 (1-Hydroxypentylidene)bisphosphonic acid P,P-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 15.72/27.62 ppm, J=31.0 Hz; D₂O).
- (1-Hydroxypentylidene)bisphosphonic acid P',P'-diethyl ester from the corresponding P,P-dimethyl P',P'-diethyl ester (31-P NMR 12.30/28.70 ppm, J=27.1 Hz; D₂O).
- 30 (1-Hydroxy-1-cyclohexylmethylidene)bisphosphonic acid P,P-dimethyl ester from the corresponding tetramethyl ester.

Example 2

- 35 Preparation of (1-hydroxypentylidene)bisphosphonic acid monoisopropyl ester
- [0072] The P,P-dimethyl P',P'-diisopropyl ester of (1-hydroxypentylidene)bisphosphonic acid (0.02 moles) was dissolved in dichloromethane and to the solution was added slowly at room temperature bromotrimethylsilane (0.062 moles). The solution was mixed at room temperature for 3 hours, whereafter the solvent was evaporated at reduced pressure. The evaporation residue was dissolved in a small amount of methanol, and the solution was evaporated (31-P NMR 17.72/22.76 ppm, J=27.1 Hz; D₂O).
- 40 [0073] In the same manner may be prepared:
- 45 (1-Hydroxyethylidene)bisphosphonic acid monoisopropyl ester from the corresponding P,P-dimethyl P',P'-diisopropyl ester (31-P NMR 18.36/23.04 ppm, J=28.8 Hz; D₂O).
- (1-Hydroxyethylidene)bisphosphonic acid monoisopropyl ester from the corresponding tetraisopropyl ester.
- 50 (1-Hydroxyethylidene)bisphosphonic acid monobutyl ester from the corresponding P,P-dimethyl P',P'-dibutyl ester (31-P NMR 18.17/22.80 ppm, J=29.6 Hz; D₂O).
- (4-Amino-1-hydroxybutylidene)bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester.
- 55 [4-(N-Phtalimidyl)-1-hydroxybutylidene]bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester.
- (1-Hydroxypentylidene)bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester (31-P NMR 16.36/24.0 ppm, J=24.5 Hz; D₂O).

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[Hydroxy(cyclohexyl)methylidene]bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester (31-P NMR 15.84/23.40 ppm, J=27.0 Hz; D₂O).

5 (1-Hydroxypentylidene)bisphosphonic acid monoethyl ester from the corresponding P,P'-dimethyl P',P'-diethyl ester (31-P NMR 18.73/20.61 ppm, J=32.3 Hz; D₂O).

(1-Hydroxy-2,2-dimethylpropylidene)bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester (31-P NMR 16.55/24.18 ppm, J=23.3 Hz; D₂O).

10 [3-(Benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid monoethylester from the corresponding tetraethyl ester.

[3-(N-phtalimidyl)-1-hydroxypropylidene]bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester.

15

Example 3

Preparation of (1-hydroxyethylidene)bisphosphonic acid trimethyl ester and its sodium salt

20 [0074] The tetramethyl ester of (1-hydroxyethylidene)bisphosphonic acid (0.02 moles) was dissolved in acetonitrile, and to the solution was slowly added chloro(tert-butyl)(dimethyl)silane (0.022 moles) dissolved in acetonitrile. The solution was mixed at 60 °C for 4 hours. The solvent was evaporated and the evaporation residue was dissolved in a small amount of water. The solution was made alkaline with a dilute sodium hydroxide solution, and the product precipitated by adding ethanol (31-P NMR 16.89/28.41 ppm, J=34.8 Hz; D₂O).

25 [0075] In a corresponding manner may be prepared

(1-Hydroxypentylidene)bisphosphonic acid trimethyl ester from the corresponding tetramethyl ester (31-P NMR 12.12/31.38 ppm, J=26.0 Hz; D₂O).

30 (1-Hydroxy-2,2-dimethylpropylidene)bisphosphonic acid trimethyl ester from the corresponding tetramethyl ester.

[3-(N-Phtalimidyl)-1-hydroxypropylidene]bisphosphonic acid trimethyl ester from the corresponding tetramethyl ester.

35 [4-(Benzyloxycarbonylamino)-1-hydroxybutylidene]bisphosphonic acid trimethyl ester from the corresponding tetramethyl ester.

[0076] By using the double amount of chloro(tert-butyl)(dimethyl)silane (0.044 moles) one can prepare

40 (1-Hydroxyethylidene)bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 21.19 ppm; D₂O).

(1-Hydroxypentylidene)bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 20.70 ppm; D₂O).

45

[4-(N-phtalimidyl)-1-hydroxybutylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 18.78 ppm; D₂O).

50 [3-(Benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

[0077] Further, in a manner corresponding to the previous example the following compounds may be prepared by using instead of chloro(tert-butyl)(dimethyl)silane for example bromo(trimethyl)silane (1 equivalent);

55 (1-Hydroxyethylidene)bisphosphonic acid P-methyl P',P'-dibutyl ester from the corresponding P,P'-dimethyl P',P'-dibutyl ester (31-P NMR 17.19/25.79 ppm, J=34.7 Hz; D₂O).

(1-Hydroxyethylidene)bisphosphonic acid P-methyl P',P'-diethyl ester from the corresponding P,P'-dimethyl P',P'-

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diethyl ester (31-P NMR 17.47/26.01 ppm, J=35.1 Hz; D₂O).

(1-Hydroxyethylidene)bisphosphonic acid P-methyl P',P'-diisopropyl ester from the corresponding P,P-dimethyl P',P'-diisopropyl ester (31-P NMR 19.10/22.44 ppm, J=37.3 Hz; D₂O).

(1-Hydroxypentylidene)bisphosphonic acid P-methyl P',P'-diethyl ester from the corresponding P,P-dimethyl P',P'-diethyl ester.

[4-(N-Phtalimidy)-1-hydroxybutylidene]bisphosphonic acid trimethyl ester from the corresponding tetramethyl ester (31-P NMR 12.01/30.89 ppm J=25.3 Hz; D₂O).

(6-Amino-1-hydroxyhexylidene)bisphosphonic acid trimethylester from the corresponding tetramethyl ester.

Example 4

Preparation of (1-hydroxyethylidene)bisphosphonic acid monomethyl ester and its trisodium salt

[0078] A toluene solution of (1-hydroxyethylidene)bisphosphonic acid (0.02 moles) and trimethyl orthoformate (0.04 moles) was mixed at 100 °C for 4 hours. The solvent and unreacted triethyl orthoformate was evaporated under reduced pressure. The evaporation residue was dissolved in ethanol. When a calculated amount (0.06 moles) of a 40 % sodium hydroxide solution was added into the ethanol solution, the product precipitated as the trisodium salt (31-P NMR 17.25/24.86 ppm, J=27.3 Hz; D₂O).

[0079] In a corresponding manner may be prepared

(3-Amino-1-hydroxypropylidene)bisphosphonic acid monoethyl ester

(6-Amino-1-hydroxyhexylidene)bisphosphonic acid monomethyl ester.

Example 5

Preparation of (1-hydroxypentylidene)bisphosphonic acid monomethyl ester and its trisodium salt

[0080] The tetramethyl ester of (1-hydroxypentylidene)bisphosphonic acid (0.01 moles) was dissolved in toluene (70 ml) and to the solution methanesulphonic acid (0.06 moles) was added. The solution was stirred while heating, and the progress of hydrolysis was followed with ³¹P NMR. The mixture was cooled and the solvent evaporated under reduced pressure. The evaporation residue was dissolved in a dilute sodium hydroxide solution. To the solution the double volume of ethanol was added and the solution was cooled. The precipitated product was filtered and dried (yield 52%, 31-P NMR 16.36/24.00 ppm, J=24.5 Hz; D₂O).

Example 6

Preparation of (1-hydroxyethylidene)bisphosphonic acid P,P'-dimethyl ester

[0081] (1-Hydroxyethylidene)bisphosphonic acid P,P'-dimethyl P,P'-bis-trimethylsilyl ester (0.01 moles) was dissolved in methanol and the solution mixed at room temperature for 2 hours. The solvent was evaporated, the evaporation residue was dissolved in a dilute sodium hydroxide solution and the disodium salt of the product was precipitated by adding a double volume of ethanol (yield 72 %, 31-P NMR 21.19 ppm; D₂O).

Example 7

Preparation of (1-hydroxypentylidene)bisphosphonic acid P,P'-dimethyl ester

[0082] The tetramethyl ester of (1-hydroxypentylidene)bisphosphonic acid (0.01 moles) was dissolved in acetone, and to the solution sodium iodide (0.023 moles) was added. The solution was mixed at room temperature for 8 hours, whereafter it was filtered. The solvent has evaporated. The product was isolated from the evaporation residue as the disodium salt as has been described in the previous example (yield 59 %, 31-P NMR 19.06 ppm; D₂O).

[0083] In a corresponding manner may be prepared

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(1-Hydroxy-2,2-dimethylpropylidene)bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 20.33 ppm; D₂O).

5 [Hydroxy(cyclohexyl)methylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester (31-P NMR 18.79 ppm; D₂O).

(1-Hydroxypentylidene)bisphosphonic acid P-methyl P'-ethyl ester from the corresponding P,P'-dimethyl P',P'-diethyl ester (31-P NMR 19.06 ppm; D₂O).

10 [4-(Benzyloxycarbonylamino)-1-hydroxybutylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

[4-(Benzyloxycarbonylamino)-1-hydroxybutylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester.

15 [3-(Benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

20 [3-(Benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester.

Example 8

Preparation of (1-hydroxyethylidene)bisphosphonic acid monomethyl ester

25 [0084] Finely ground (1-hydroxyethylidene)bisphosphonic acid (0.005 moles) was mixed with 100 ml of chloroform and to the mixture 25 ml of an appr. 2% ether solution of diazomethane were slowly added at room temperature. After the addition, the mixing was continued for 1 hour, whereafter the solution was evaporated at reduced pressure (yield 42 %, 31-P NMR 17.25/24.84 ppm, J=27.3; D₂O).

30 [0085] In a corresponding manner other mono- and diesters, for example dimethyl, mono- and diethyl and benzyl esters may be prepared by using suitable diazo reagents.

Example 9

35 Preparation of (1-hydroxypentylidene)bisphosphonic acid monomethyl ester and its trisodium salt

[0086] The tetramethyl ester of (1-hydroxypentylidene)bisphosphonic acid (0.01 moles) was slurried in a 10% hydrochloric acid solution and the solution mixed at 70 °C. The progress of the reaction was followed using 31-P NMR. After the reaction, the mixture was evaporated to dryness, the evaporation residue dissolved in a sodium hydroxide solution and the product precipitated by adding ethanol. The product was filtered and dried (yield 55%, 31-P NMR 16.36/24.00 ppm, J=24.5 Hz; D₂O).

40 [0087] In a corresponding manner [(3-dimethylamino)-1-hydroxypropylidene]bisphosphonic acid monomethyl ester may be prepared.

45 Example 10

Preparation of (4-amino-1-hydroxybutylidene)bisphosphonic acid P,P'-diethyl ester disodium salt

50 [0088] [4-(Benzyloxycarbonylamino)-1-hydroxybutylidene]bisphosphonic acid P,P'-diethyl ester (1 g) was dissolved in ethanol (30 ml) and hydrogenated at a pressure of 35 psi using as a catalyst 5% palladium-carbon (0.1 g). The catalyst was filtered off and the pH of the filtrate was adjusted to pH 7-7.5 with a dilute sodium hydroxide solution. The solution was evaporated and the evaporation residue was treated with acetone. The product was filtered and dried (yield 65%).

[0089] In the same manner may be prepared

55 (3-Amino-1-hydroxypropylidene)bisphosphonic acid P,P'-dimethyl ester from [3-(benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid P,P'-dimethyl ester.

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(3-Amino-1-hydroxypropylidene)bisphosphonic acid P,P'-diethyl ester from [3-(benzyloxycarbonylamino)-1-hydroxypropylidene]bisphosphonic acid P,P'-diethyl ester.

(4-Amino-1-hydroxybutylidene)bisphosphonic acid P,P'-dimethyl ester from [4-(benzyloxycarbonylamino)-1-hydroxybutylidene]bisphosphonic acid P,P'-dimethyl ester.

Example 11

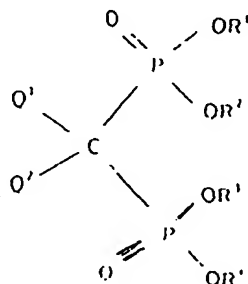
Preparation of [(4-dimethylamino)-1-hydroxybutylidene]bisphosphonic acid monoethyl ester and its trisodium salt

[0090] A mixture of [(4-dimethylamino)-1-hydroxybutylidene]bisphosphonic acid P-ethyl [P,P',P'-tris(trimethylsilyl)] ester (0.01 moles) and dilute hydrochloric acid was stirred at 0°C for 0.5 hours. To the filtered solution dilute sodium hydroxide was added (in excess 0.02 moles) and the product was precipitated with ethanol.

[0091] In a corresponding manner [(3-methyl(pentyl)amino)-1-hydroxypropylidene]bisphosphonic acid monomethyl ester may be prepared.

Claims

1. Bisphosphonic acid derivatives having the formula I



wherein

one or two of the groups

R¹, R², R³ and R⁴ are independently straight or branched, C₁-C₁₀-alkyl, and the remaining groups R¹, R², R³ and R⁴ are hydrogen,

Q¹ is hydroxyl,

Q² is straight or branched C₁-C₁₀-alkyl, cyclohexyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-aminoethyl, 3-amino-propyl, (3-dimethylamino)propyl, or 5-aminopentyl, including the stereoisomers, such as the geometrical isomers and the optically active isomers, of the compounds, as well as the pharmacologically acceptable salts of the compounds.

2. Compound of Claim 1, whereing one or two of R¹-R⁴ have the meaning of methyl, ethyl or isopropyl.

3. Compound of Claim 1 or 2, wherein Q² is methyl, ethyl, propyl, isopropyl, 2,2-dimethylpropyl or butyl.

4. Mono- or dimethyl-, mono- or diethyl, mono- or diisopropylesters or corresponding mixed diesters of [(4-methyl(pentyl)amino)-1-hydroxybutylidene]bisphosphonic acid.

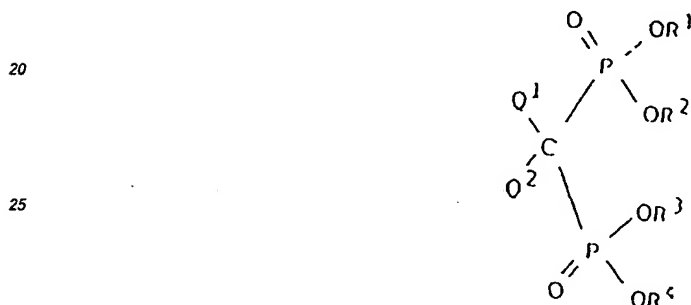
5. A compound which is

(1-hydroxyethylidene)bisphosphonic acid monomethyl and monoethyl ester,
(1-hydroxypentylidene)bisphosphonic acid monomethyl ester,

- (1-hydroxyethylidene)bisphosphonic acid dimethyl and diethyl ester,
 (2,2-dimethyl-1-hydroxypropylidene)bisphosphonic acid monomethyl ester,
 [hydroxy(cyclohexyl)methylidene]bisphosphonic acid monomethyl ester,
 (1,3-dihydroxypropylidene)bisphosphonic acid monoethyl ester,
 5 (3-amino-1-hydroxypropylidene)bisphosphonic acid monomethyl and monoethyl ester,
 (4-amino-1-hydroxybutylidene)bisphosphonic acid monomethyl and monoethyl ester,
 (6-amino-1-hydroxyhexylidene)bisphosphonic acid monomethyl- and monoisopropyl ester,
 (3-amino-1-hydroxypropylidene)bisphosphonic acid P,P'-dimethyl and P,P'-diethyl ester,
 (4-amino-1-hydroxybutylidene)bisphosphonic acid P,P'-dimethyl- and P,P'-diethyl ester,
 10 [(4-dimethylamino)-1-hydroxybutylidene]bisphosphonic acid monoethyl ester,
 [(3-methyl(pentyl)amino)-1-hydroxypropylidene]bisphosphonic acid monomethyl ester.

6. Process for the preparation of the compounds according to the Claim 1, characterized in that

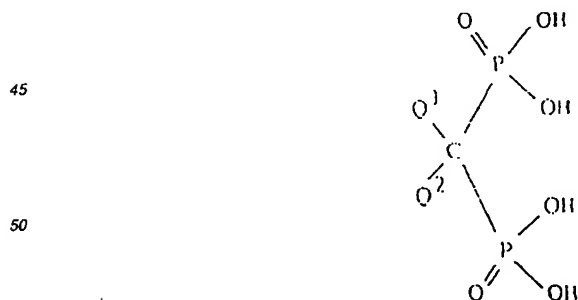
- 15 a) a methylenebisphosphonic acid tetraester of the formula II



in which formula Q¹ and Q² have the same meaning as in the Claim 1, and R¹, R², R³ and R⁴ have the same meaning as in the Claim 1, or triloer alkyl silyl, except hydrogen, is selectively hydrolysed

- 35 - to a diester corresponding to the formula I, wherein two of the groups R¹, R², R³ and R⁴ have the meaning of hydrogen, or a salt thereof, or
 - to a monoester corresponding to the formula I, wherein three of the groups R¹, R², R³ and R⁴ have the meaning of hydrogen, or a salt thereof, or

- 40 b) a bisphosphonic acid of the formula



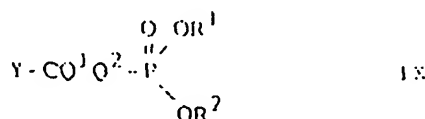
or a metal or ammonium salt thereof, or the corresponding acid tetrachloride, wherein Q¹ and Q² have the same meaning as in the Claim 1, is esterified selectively by reacting the same with an esterification reagent corresponding to the desired groups R¹, R², R³ and R⁴,

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- to a monoester corresponding to the formula I, wherein three of the groups R^1 , R^2 , R^3 and R^4 have the meaning of hydrogen, or
- to a diester corresponding to the formula I, wherein two of the groups R^1 , R^2 , R^3 and R^4 have the meaning of hydrogen,

or to the corresponding ester salts of the said partial esters, or

c) a phosphonate having the formula



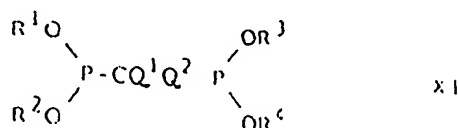
is reacted with an activated phosphate or a hydrogen phosphonate corresponding to the formula X



wherein in the formulas Y is hydrogen, hydroxy or halogen or other leaving group, Z is hydrogen, halogen, acyloxy, sulphonyloxy, alkoxy or aryloxy, and R^1 to R^4 and Q^1 and Q^2 have the same meaning as before, or Q^1 and Q^2 form a double-bonded oxygen, or is reacted with a phosphite corresponding to the formula X, or

d) a bisphosphonate corresponding to the formula I, which instead of Q^2 has a carbanion site, is reacted with ω -leaving group substituted Q^2 , or a bisphosphonate corresponding to the formula I, which instead of Q_2 contains a leaving group, is reacted with a ω -carbanion corresponding to Q^2 , or a (Q^2-C_1) - ω -carbanion is added by Michael addition in alkylidenebisphosphonates, or

e) a bisphosphonite compound having the formula

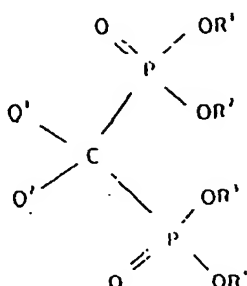


wherein R^1 , R^2 , R^3 and R^4 and Q^1 and Q^2 have the same meaning as in the formula I, or the corresponding hydrogen phosphonate compound, is oxidized to a compound of the formula I, and if desired, the partial ester acids obtained according to a) to e) are converted to partial ester salts, or the partial ester salts obtained are converted to the partial ester acids, and/or, if desired, a compound according to the formula I obtained is converted into some other compound according to the formula I by hydrolyzing, esterification or transesterification.

7. Pharmaceutical composition characterized in that it as the active agent contains a compound according to the Claim 1, 2, 3, 4 or 5.

Patentansprüche

1. Bisphosphonsäurederivate der Formel I



20 worin eine oder zwei der Gruppen R^1 , R^2 , R^3 und R^4 unabhängig voneinander geradkettiges oder verzweigtes C_1 - C_{10} -Alkyl bedeuten, und die verbleibenden Gruppen R^1 , R^2 , R^3 und R^4 Wasserstoff bedeuten,

Q^1 Hydroxyl bedeutet,

25 Q^2 geradkettiges oder verzweigtes C_1 - C_{10} -Alkyl, Cyclohexyl, 2-Hydroxyethyl, 3-Hydroxypropyl, 2-Aminoethyl, 3-Aminopropyl, (3-Dimethylamino)propyl, oder 5-Aminopentyl bedeutet, eingeschliesslich der Stereoisomere, wie der geometrischen Isomere und der optisch aktiven Isomere der Verbindungen sowie der pharmakologisch annehmbaren Salze der Verbindungen.

30 2. Verbindung nach Anspruch 1, in der eine oder zwei der Gruppen R^1 - R^4 Methyl, Ethyl oder Isopropyl bedeuten.

3. Verbindung nach Anspruch 1 oder 2, in der Q^2 Methyl, Ethyl, Propyl, Isopropyl, 2,2-Dimethylpropyl oder Butyl bedeutet.

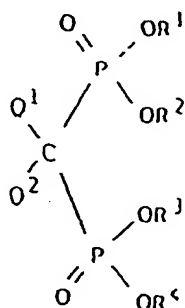
35 4. Mono- oder Dimethyl-, Mono- oder Diethyl-, Mono- oder Diisopropylester oder entsprechende Mischdiester von [(4-Methyl(pentyl)amino)-1-hydroxybutyliden]bisphosphonsäure.

5. Eine Verbindung, die

40 Monomethyl- und Monoethylester von (1-Hydroxyethyliden)bisphosphonsäure,
 Monomethylester von (1-Hydroxypentyliden)bisphosphonsäure,
 Dimethyl- und Diethylester von (1-Hydroxyethyliden)bisphosphonsäure,
 Monomethylester von (2,2-Dimethyl-1-hydroxypropyliden)bisphosphonsäure,
 Monomethylester von [Hydroxy(cyclohexyl)methyliden]bisphosphonsäure,
 45 Monoethylester von (1,3-Dihydroxypropyliden)bisphosphonsäure,
 Monomethyl- und Monoethylester von (3-Amino-1-hydroxypropyliden)bisphosphonsäure,
 Monomethyl- und Monoethylester von (4-Amino-1-hydroxybutyliden)bisphosphonsäure,
 Monomethyl- und Monoisopropylester von (6-Amino-1-hydroxyhexyliden)bisphosphonsäure,
 P, P'-Dimethyl- und P, P'-Diethylester von (3-Amino-1-hydroxypropyliden)bisphosphonsäure,
 50 P,P-Dimethyl- und P,P'-Diethylester von (4-Amino-1-hydroxybutyliden)bisphosphonsäure,
 Monoethylester von [(4-Dimethylamino)-1-hydroxybutyliden]bisphosphonsäure,
 Monomethylester von [(3-Methyl(pentyl)amino)-1-hydroxypropyliden]bisphosphonsäure.

6. Verfahren zur Herstellung der Verbindungen nach Anspruch 1, dadurch gekennzeichnet, dass

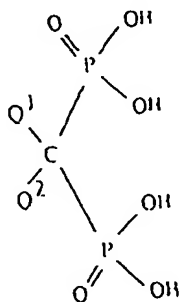
a) ein Methylenbisphosphonsäuretetraester der Formel II



in welcher Formel Q¹ und Q² dieselben Bedeutungen wie im Anspruch 1 haben, und R¹, R², R³ und R⁴ dieselben Bedeutungen wie im Anspruch 1 haben, oder Triniederalkylsilyl, mit Ausnahme von Wasserstoff, bedeuten,

- zu einem Diester entsprechend der Formel I, worin zwei der Gruppen R¹, R², R³ und R⁴ Wasserstoff bedeuten, oder zu dessen Salz, oder
- zu einem Monoester entsprechend der Formel I, worin drei der Gruppen R¹, R², R³ und R⁴ Wasserstoff bedeuten, oder zu dessen Salz selektiv hydrolysiert wird, oder

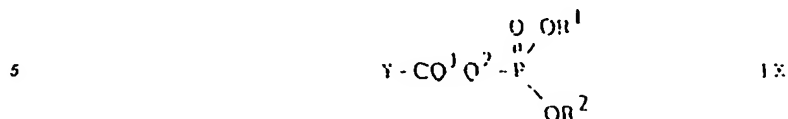
b) eine Bisphosphonsäure der Formel



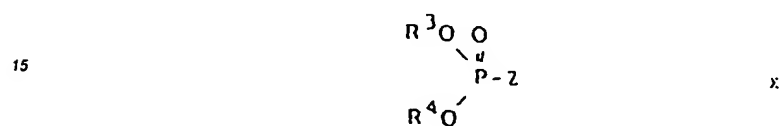
oder deren Metall- oder Ammoniumsalz, oder das entsprechende Säuretetrachlorid, in welcher Formel Q¹ und Q² dieselben Bedeutungen wie im Anspruch 1 haben, durch Umsetzung derselben mit einem den gewünschten Gruppen R¹, R², R³ und R⁴ entsprechenden Veresterungsreagenz

- zu einem Monoester entsprechend der Formel I, worin drei der Gruppen R¹, R², R³ und R⁴ Wasserstoff bedeuten, oder
- zu einem Diester entsprechend der Formel I, worin zwei der Gruppen R¹, R², R³ und R⁴ Wasserstoff bedeuten, oder zu den entsprechenden Estersalzen der genannten Partialester selektiv verestert wird, oder

c) ein Phosphonat der Formel



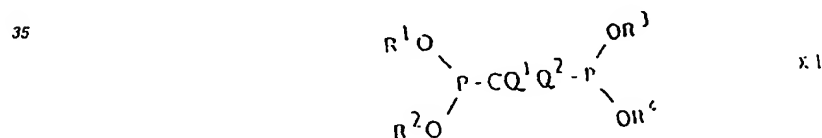
10 mit einem aktivierten Phosphat oder einem Wasserstoffphosphonat entsprechend der Formel



20 umgesetzt wird, in welchen Formeln Y Wasserstoff, Hydroxy oder Halogen oder eine andere abgehende Gruppe bedeutet, Z Wasserstoff, Halogen, Acyloxy, Sulfonyloxy, Alkoxy oder Aryloxy bedeutet, und $R^1 - R^4$ und Q^1 und Q^2 dieselben Bedeutungen wie oben haben, oder Q^1 und Q^2 einen Sauerstoff mit Doppelbindung bilden, oder mit einem Phosphit entsprechend der Formel X umgesetzt wird, oder

25 d) ein Bisphosphonat entsprechend der Formel I, worin anstelle von Q^2 eine Carbanionstelle steht, mit durch ω -abgehende Gruppe substituiertem Q^2 umgesetzt wird, oder ein Bisphosphonat entsprechend der Formel I, die anstelle von Q^2 eine abgehende Gruppe enthält, mit einem dem Q^2 entsprechenden ω -Carbanion umgesetzt wird, oder ein $(Q^2-C_1)\omega$ -Carbanion durch Michael-Addition an Alkylidenbisphosphonaten angefügt wird, oder

30 e) eine Bisphosphonitverbindung der Formel

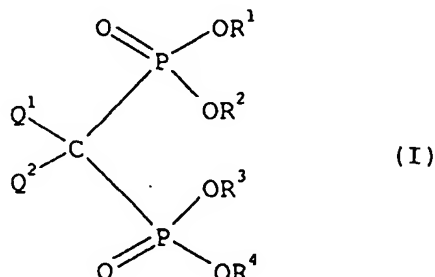


40 worin R^1, R^2, R^3 und R^4 und Q^1 und Q^2 dieselben Bedeutungen wie in der Formel I haben, oder die entsprechende Wasserstoffphosphonatverbindung zu einer Verbindung der Formel I oxydiert wird, und wenn erwünscht, die gemäss den Schritten a) bis e) erhaltenen Partialestersäuren in Partialestersalze umgewandelt werden, oder die erhaltenen Partialestersalze in Partialestersäuren umgewandelt werden, und/oder, wenn erwünscht, eine erhaltene Verbindung der Formel I durch Hydrolysierung, Veresterung oder Umesterung in eine andere Verbindung der Formel I umgewandelt wird.

50 7. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, dass sie als den Wirkstoff eine Verbindung nach Anspruch 1, 2, 3, 4 oder 5 enthält.

Revendications

55 1. Dérivés d'acide bisphosphonique de formule I



15 dans laquelle
un ou deux des groupes R^1 , R^2 , R^3 et R^4 sont chacun indépendamment un alkyle en C_1 - C_{10} à chaîne linéaire ou ramifiée, et les groupes restant R^1 , R^2 , R^3 et R^4 sont H,

20 Q^1 est OH,

Q^2 est alkyle en C_1 - C_{10} à chaîne linéaire ou ramifiée, cyclohexyle, 2-hydroxyéthyle, 3-hydroxypropyle, 2-aminoéthyle, 3-aminopropyle, (3-diméthylamino)propyl ou 5-aminopentyle,
y compris leurs stéréoisomères, tels que les isomères géométriques et les isomères optiquement actifs, ainsi que leurs sels pharmacologiquement acceptables.

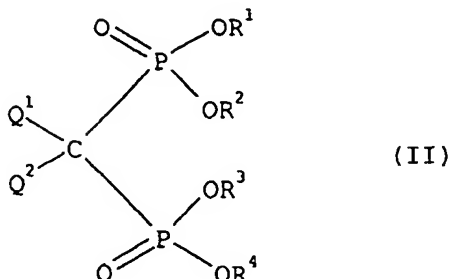
- 25 2. Composé suivant la revendication 1, dans lequel un ou deux des R^1 - R^4 représentent méthyle, éthyle ou isopropyle.
- 30 3. Composé suivant la revendication 1 ou 2, dans lequel Q^2 est méthyle, éthyle, propyle, isopropyle, 2,2-diméthylpropyle ou butyle.
4. Mono- ou diméthyl, mono- ou diéthyl, mono- ou diisopropyl esters ou diesters mixtes correspondants de l'acide [(4-méthyl(pentyl)amino)-1-hydroxybutylidène]bisphosphonique.

- 35 5. Composé qui est un

acide (1-hydroxyéthylidène)bisphosphonique monométhyl ou monoéthyle ester,
acide (1-hydroxypentylidène)bisphosphonique monométhyl ester,
acide (1-hydroxyéthylidène)bisphosphonique diméthyl ou diéthyl ester,
40 acide (2,2-diméthyl-1-hydroxypropylidène)bisphosphonique monométhyl ester,
acide [hydroxy(cyclohexyl)méthylidène]bisphosphonique monométhyl ester,
acide (1,3-dihydroxypropylidène)bisphosphonique monoéthyl ester,
acide (3-amino-1-hydroxypropylidène)bisphosphonique monométhyl ou monoéthyl ester,
acide (4-amino-1-hydroxybutylidène)bisphosphonique monométhyl ou monoéthyl ester,
acide (6-amino-1-hydroxyhexylidène)bisphosphonique monométhyl ou monoisopropyl ester,
45 acide (3-amino-1-hydroxypropylidène)bisphosphonique P,P'-diméthyl ou P,P'-diéthyl ester,
acide (4-amino-1-hydroxybutylidène)bisphosphonique P,P'-diméthyl- ou P,P'-diéthyl ester,
acide [(4-diméthylamino)-1-hydroxybutylidène]bisphosphonique monoéthyl ester, ou
acide [(3-méthyl(pentyl)amino)-1-hydroxypropylidène]bisphosphonique monométhyl ester.

- 50 6. Procédé pour la préparation des composés de formule I selon la revendication 1, caractérisé en ce que

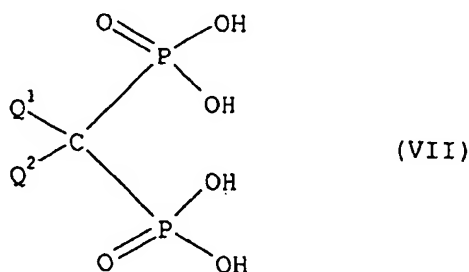
a) on hydrolyse sélectivement un acide méthylènebisphosphonique tétraester de formule II



dans laquelle Q^1 et Q^2 sont définis comme indiqué dans la revendication 1, et les R^1 , R^2 , R^3 et R^4 ont la même signification que dans la revendication 1 sauf qu'ils sont différents de H, ou représentent un groupe tri(alkyle inférieur)silyle, en

- un diester correspondant de formule I, où deux des groupes R^1 , R^2 , R^3 et R^4 représentent H, ou l'un de ses sels, ou
- un monoester correspondant de formule I, où trois des groupes R^1 , R^2 , R^3 et R^4 représentent H, ou l'un de ses sels, ou

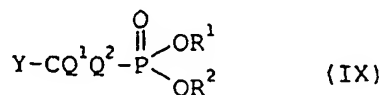
b) on estérifie sélectivement un acide bisphosphonique de formule



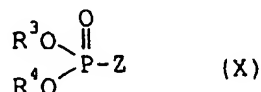
l'un de ses sels métalliques, l'un de ses sels d'ammonium, ou le tétra(chlorure d'acide) correspondant, dans laquelle Q^1 et Q^2 sont définis comme indiqué dans la revendication 1, par réaction avec un agent d'estérification correspondant pour les groupes R^1 , R^2 , R^3 et R^4 désirés, en

- un monoester correspondant de formule I, où trois des groupes R^1 , R^2 , R^3 et R^4 représentent H, ou l'un de ses sels, ou
- un diester correspondant de formule I, où deux des groupes R^1 , R^2 , R^3 et R^4 représentent H, ou l'un de ses sels, ou en sels d'ester correspondant desdits esters partiels, ou

c) on fait réagir un phosphonate de formule



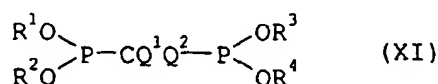
avec un phosphate activé ou un hydrogénophosphate de formule X



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10 dans lesquelles Y est hydrogène, hydroxy ou halogène ou un autre groupe clivable, Z est hydrogène, halogène, acyloxy, sulfonyloxy, alkoxy ou aryloxy, et les groupes R¹ à R⁴ et Q¹ et Q² sont définis comme indiqué dans la revendication 1, ou Q¹ et Q² forment une double liaison =O
ou avec un phosphite correspondant à la formule X, ou
d) on fait réagir un bisphosphonate correspondant à la formule I, qui a au lieu de Q² un site carbanion, avec un
15 Q² substitué par un ω-groupe clivable, ou un bisphosphonate correspondant à la formule I, qui au lieu de Q² contient un groupe clivable, avec un ω-carbanion correspondant à Q², ou un (Q²-C₁)-ω-carbanion est ajouté selon une réaction d'addition de Michael dans des alkylidènebisphosphonates, ou
e) on oxyde un composé bisphosphonite de formule

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dans laquelle les groupes R¹, R², R³ et R⁴ et Q¹ et Q² sont définis comme indiqué dans la revendication 1, ou le composé hydrogénophosphonate correspondant, en un composé de formule I, et
si nécessaire, les acides obtenus sous forme d'ester partiel selon les étapes a) à e) sont convertis en sels d'ester partiel, ou les sels d'ester partiel sont convertis en acides sous forme d'ester partiel, et/ou si nécessaire
30 un composé de formule I est converti en un autre composé de formule I par hydrolyse, estérification ou transestérification.

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7. Composition pharmaceutique, caractérisée en ce qu'elle contient, en tant qu'ingrédient actif, un composé selon la revendication 1, 2, 3, 4 ou 5.

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